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No Needles, No Pain - Edible Vaccines as an Alternative to Traditional Vaccination Methods

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Abstract

Edible vaccines represent an innovative approach to immunization, offering a promising alternative to traditional injectable vaccines. Produced in genetically modified plants or microorganisms, these vaccines are administered orally, eliminating the need for needles, cold chain storage, and trained medical personnel. They stimulate both mucosal and systemic immunity, providing early protection against pathogens at entry points such as the gastrointestinal tract. Key advantages include lower production costs, ease of distribution, and higher public acceptance, particularly in children and resource-limited settings. A notable success is the plant-based COVID-19 vaccine COVIFENZ®, developed using virus-like particles (VLPs) from *Nicotiana benthamiana*, which has been approved in Canada.
Despite their potential, edible vaccines face challenges, including dosage standardization, risk of immune tolerance, antigen degradation in the digestive system, and public skepticism toward genetically modified organisms. Additionally, heat-sensitive plant-based vaccines may lose efficacy if cooked. Ongoing research aims to optimize adjuvants, enhance antigen stability, and expand applications beyond infectious diseases, including autoimmune therapies.
Edible vaccines hold significant promise for global health, particularly in developing countries with limited healthcare infrastructure. Their scalability, cost-effectiveness, and needle-free administration could revolutionize vaccination strategies, especially during

pandemics. While further clinical and regulatory advancements are needed, edible vaccines may soon transform preventive medicine, making immunization more accessible and acceptable worldwide.

Keywords: edible vaccines, prevention of infectious diseases, oral immunization, vaccination innovations, plant-based vaccines

Introduction

Vaccination is one of the most effective and groundbreaking methods in the fight against infectious diseases, which have been a threat to human health for centuries. Thanks to the invention of vaccines, many once deadly diseases, such as smallpox, polio, diphtheria, tetanus, rubella and measles, have been virtually eliminated or significantly reduced on a global scale [1,2,3,4,5,6,7,8,9]. Over the past decades, vaccinations have saved millions of lives, and their introduction is the basis of modern medicine and public health. Thanks to universal access to vaccines, the number of illnesses, hospitalizations and deaths has been reduced, resulting in an improved quality of life worldwide [3,4,8]. Despite progress in vaccination programs, infectious diseases continue to be a serious health problem in developing countries, contributing to significant morbidity and mortality, especially among children and people with limited access to health care [3,6,7,10]. Despite these undeniable successes, traditional vaccination methods have a number of shortcomings that make their widespread use difficult, especially in regions with limited access to appropriate health infrastructure. They require precise administration by trained personnel, appropriate storage and transport. High production costs are also a problem [1,4,5,7,8,9,10,11,12,13,14,15]. These factors can be a serious barrier to the spread of preventive vaccination, especially in developing countries [2,6,7,8,9,10,13,14,16]. In response to these challenges, scientists and public health specialists are increasingly looking for innovative solutions that could make vaccinations more accessible, convenient and effective. In this context, edible vaccines are giving hope and can be a real revolution in the approach to preventive health care [1,2,3,4,5,14,17,18]. Edible vaccines are a technology that allows the administration of vaccines in the form of consumed products, such as plants or microorganisms that contain genetically modified proteins that induce an immune response [1,2,3,4,5,6,8,9,10,11,12,13,14,17,19,20]. This innovative method can not only contribute to greater acceptance of vaccinations, but also increase their availability in places where traditional vaccines do not reach in sufficient quantities. In the context of global health challenges, edible vaccines can become a key element of health prevention, especially in developing countries [3,6,7,10,14,17]. The aim of this article is to analyze the potential of edible vaccines as an innovative solution in the field of public health that can improve the availability of vaccines worldwide. The paper aims to present the benefits of their use, the challenges that face the development of this technology, and considers how edible vaccines can change global vaccination strategies and contribute to the improvement of public health worldwide.

Limitations of traditional vaccination methods

Despite their widespread use, traditional vaccines present various limitations [1]. One of the key challenges faced by conventional vaccine platforms is the cost-intensive manufacturing process and the requirement for multiple-dose regimens, which additionally raises the overall cost [6,7,16]. Another constraint of traditional vaccines is their mode of administration. These formulations are predominantly delivered parenterally, which requires the involvement of qualified medical staff. Furthermore, vaccines delivered parenterally may occasionally result in adverse reactions, such as site-specific inflammation at the injection site, elevated body temperature and infrequently hypersensitivity responses [1,7]. It is worth noting the challenge posed by the necessity of maintaining proper storage conditions for conventional vaccines. These vaccines frequently require cold-chain storage, and non-compliance with these condition, especially in transit, may compromise their effectiveness [1,4]. Although parenterally administered vaccines can generate strong systemic antibody responses, they are insufficient in generating strong mucosal immunity, which represents an additional limitation [1,7]. These constraints underscore the need to develop and investigate alternative approaches to conventional vaccination.

Edible vaccines

Edible vaccines are a modern form of immunization in which the active ingredient of the vaccine (antigen) is produced by edible plants or microorganisms and then administered orally. Unlike traditional vaccines, which require injection, edible vaccines are simply consumed, e.g. in the form of fruits, vegetables (e.g. bananas, potatoes, lettuce), algae, yeast, insect cells and lactic acid bacteria [1,2,3,4,5,6,7,8,9,10,12,13,14,15,17,19,20]. Edible vaccines work by introducing proteins from a pathogen (e.g. a virus or bacteria) into the body, which stimulates the immune system to produce antibodies without causing disease [1,2,3,4,5,6,8,9,12,13,14,15,17,19,20]. They can be particularly useful in regions where access to traditional vaccines is limited. However, they are still the subject of intensive research, and their widespread application requires overcoming numerous technological and regulatory challenges [3,4,6,7,8,9,10,12,13,14,15,16,17,20].

Mechanism of action of edible vaccines

Edible vaccines, upon contact with the gastrointestinal mucosa, induce both a mucosal and systemic response. The oral mucosal immune system (MIS) is one of the first lines of the body's immune defense. Both B and T lymphocytes participate in the activation of oral mucosal immunity. Activation of lymphocytes enables the development of immunological memory cells, which play an important role in the rapid neutralization of emerging pathogens [1,2,8,13,14]. The effectiveness of mucosal immunization is based primarily on the fact that the mucosa serves as the largest organ of the immune system in the human body [3,13]. When an oral vaccine is ingested, the antigens contained in it reach the intestine, where their recognition by the immune system begins. Antigens in the small intestine are captured by Microfold (M) cells and macrophages. Then, antigens are transferred to antigen-presenting cells (APCs), which are located in Peyer's patches. APCs include dendritic cells (DCs), which are most effective in presenting antigens. This leads to the activation of T lymphocytes into effector cells, which leads to the initiation of an adaptive immune response. At the same time, T lymphocytes activate B lymphocytes, which differentiate in the mesenteric nodes into plasma cells capable of producing IgA antibodies [1,2,4,8,9,13,17]. After penetrating the mucosal epithelium, IgA antibodies bind to secretory components present in the membrane, forming complexes known as secretory IgA (sIgA). This allows interactions with the bound antigen and eradication of pathogens in the body [1,13]. To be effective, an edible vaccine should stimulate T and B lymphocyte responses to produce long-term memory cells [4]. Obstacles that affect vaccine efficacy are the harsh environmental conditions of the gastrointestinal tract. Antigens in such an environment can be easily and rapidly degraded [13]. However, the main challenge of oral vaccines is their tolerability [1,2]. Antigens administered orally in the absence of inflammation may be perceived by the immune system as harmless. In this situation, antigens are presented to T lymphocytes by immature DC cells, which, through the secretion of IL-10 cytokines or direct contact with T lymphocytes, lead to the development of tolerance. In this way, the body learns to ignore antigens, thereby weakening the immune system's response [1,4,9]. This mechanism is the basis for research on the introduction of edible vaccines for the treatment of autoimmune diseases. Through oral administration, they aim to use the mechanism of oral tolerance and thus teach the body to tolerate antigenic proteins [4].

Types of edible vaccines

In resource-limited settings, edible vaccines present a practical and economical alternative due to their low production costs and minimal storage demands. Plant-derived vaccines bypass the need for sophisticated cell culture systems used in conventional vaccines. Researchers are also turning to other edible systems, including insect-derived cells, algae, yeast and probiotic bacteria. Certain plants, such as alfalfa, are predominantly used as platforms for the production of veterinary vaccines. Table 1 presents a summary of the main oral vaccine types and their characteristics [1,21].

Table 1. Summary of main edible vaccine types and their characteristics [1,2,4,8,15]

Type of edible vaccines	**Vaccine Model Species**	**Short overview**
	Potato	- Potential vaccine production model for: Diphtheria, Hepatitis B, Tetanus, Norwalk virus infection - easy genetic modification and propagation, storage without refrigeration - heat from cooking causes antigen denaturation, needs to be cooked before eating
	Banana	- Potential vaccine production model for: Hepatitis B - does not require cooking, protein

Plant-Based Oral Vaccines		stability maintained post-cooking, - long maturation period, rapid spoilage after ripening
	Rice (*Oryza sativa)*	- Potential vaccine production model for: Hepatitis B, infectious conditions include cholera - potential to treat allergies - may improve public health in rice-consuming regions
	Carrots	- Potential vaccine production model for: Escherichia coli infections, HIV, Helicobacter pylori infection, Measles virus
	Lettuce	- Potential vaccine production model for: Escherichia coli infections, hepatitis B, SARS-CoV-2 - potential of lettuce as a flexible platform for vaccine antigen production
	Tomato	- Potential vaccine production model for: Severe acute respiratory syndrome (SARS), Norwalk virus infection, Hepatitis B, Pneumonia, Cholera, Bubonic plague, Septicaemia, Alzheimer's disease - it deteriorates easily
	Tobacco	- Potential vaccine production model for: Norwalk virus infection, Hepatitis B, Coccidiosis, Cholera, Tetanus, HPV infections, Multiple

		sclerosis - increased production yield than leaf-based techniques, no need for cold storage, simplified purification, fast growth
	Maize	- Potential vaccine production model for: Influenza, Hepatitis B, Newcastle disease virus (NDV) infection, HIV - consuming corn foods like corn flakes or chips could enhance the efficacy of corn-derived vaccines
Algae-Based Oral Vaccines	Chlamydomonas reinhardtii	- Potential vaccine production model for: HPV infections, Hepatitis B, Foot-and-mouth disease (FMDV) - high antigen output from chloroplasts - stable at room temperature for up to 20 months, safe growing in closed systems, cheap and easy to produce - lack of glycosylation in chloroplasts may reduce antigen effectiveness
Insect Cell-Based Oral Vaccines	Silkworms (Bombyxmori larvae or pupae)	- growing progress in Baculovirus Expression Vector Systems (BEVS) and the use of insect cell cultures as an alternative platform for manufacturing recombinant proteins, including eatible vaccines - potential use in gene therapy
		- Potential vaccine production model for: Infuenza, HPV infections,

Whole Yeast Cell-Derived Oral Vaccines	Saccharomyces cerevisiae,	Actinobacillus pleuropneumoniae infection, Hepatitis C, Hepatitis B - GRAS status (Generally Recognized As Safe) - cell wall enables antigen stability in gut - excessive glycosylation can affect protein function
Probiotic Bacteria-Based Oral Vaccines	Lactic acid bacteria (LABs) - Lactobacillus spp and Bacillus subtilis	- Potential vaccine production model for: Helicobacter pylori infection (urease B) - LAB naturally enhances immune responses and modulates the immune system.

Advantages of edible vaccines

Recent efforts to overcome the limitations of injectable vaccines have led to the development of new delivery strategies integrated with cutting-edge formulations and manufacturing systems [5]. One of them is edible vaccine strategy. As far as advantages are concerned, plant vaccines are likely to be cost-effective in production and easily scalable, as demonstrated by the biopharmaceutical sector [5]. Unlike traditional vaccines, edible vaccines do not need complex systems for production, purification, sterilization, packaging, or distribution, leading to reduced overall expenses [4,22]. Additionally, distributing and storing edible vaccines is simpler than traditional vaccines, allowing for global immunization without relying on constant refrigeration. [4,23]. Another benefit of this strategy is that plant cells, with their strong cell walls, can shield the antigen from degradation [5]. The expression of antigens in seeds contributes to long-term stability and durability, making it a key benefit of edible vaccines [4,24]. When using edible vaccines, there is no need for syringes or needles, which reduces the risk of infection [7]. This type of vaccines are highly accepted, especially by children, and their oral administration minimizes the need for trained healthcare workers [7, 25].

Injectable vaccines trigger strong humoral immunity but weak cellular responses and lack mucosal protection, which is crucial for blocking infections at early stages. Edible vaccines, on the other hand, have the ability to activate both mucosal and systemic immunity, making them a promising option. [5,7,13].

An interesting development is the increasing use of edible vaccines in women to help protect their babies—either before birth via the transfer of maternal antibodies through the placenta, or after birth through breast milk to provide immunity to the infant. Edible vaccines could help protect infants from various infections, including group B Streptococcus and respiratory syncytial virus [7,25].

Challenges of edible vaccines

There are several obstacles that need to be resolved to make edible vaccines both effective and reliably beneficial [13]. One limitation of edible vaccines is the uncertainty in determining the appropriate dosage, which may require multiple administrations and, as a result, increase the overall cost of their use [4,13]. What is more, insufficient doses may fail to trigger an adequate immune response, while repeated or high doses of antigen-containing plants could overstimulate the immune system, potentially resulting in immune tolerance to the vaccine peptides or proteins [13,17,26]. Additionally, a key discussion point regarding oral vaccines is the occurrence of “oral tolerance”, which is caused by T cells and results in a reduced specific immune reaction to antigens that have been previously introduced via oral ingestion [4,27,28].

Another challenge is that some plants or parts of plants, such as potatoes, are usually cooked, as eating them raw is uncommon and heat can degrade or break down many of the proteins or peptides they contain. [13].

In addition, when developing edible vaccines, it's crucial to take into account the specific features of the gastrointestinal tract, where factors such as digestive enzymes, bile salts, low pH and limited absorption capacity may interfere with generating an effective immune response [17].

COVID-19 plant-based vaccines

During the COVID-19 pandemic, scientists have been working to create a SARS-CoV-2 vaccine that would effectively combat the spread of the disease. One idea turned out to be plant-based vaccines. Extensive research on coronavirus vaccines has established the spike (S) glycoprotein as the primary target for inducing protective antibodies. This viral component has become the foundation for developing COVID-19 vaccines, with innovative approaches focusing on plant-based expression systems. By incorporating the gene encoding the spike protein or its subunits into edible plants such as lettuce, tomatoes, or cucumbers through plant expression vectors, researchers aim to create transgenic crops that could serve as orally administered vaccines when consumed raw. This strategy has gained significant attention, with numerous research groups and biotechnology companies actively pursuing plant-based vaccine development against SARS-CoV-2 [7,8,9,12,14,20].

A notable breakthrough was achieved by Medicago, a Canadian biopharmaceutical company, which developed virus-like particles (VLPs) containing the SARS-CoV-2 spike protein within just 20 days of obtaining the viral sequence. Their innovative platform utilizes Agrobacterium-mediated transformation of Nicotiana benthamiana, a close relative of tobacco, to produce non-infectious VLPs that mimic the coronavirus structure without containing genetic material. These plant-derived VLPs, consisting of the viral spike protein embedded in plant lipid membranes. The platform's credibility is further supported by Medicago's prior success in developing plant-based VLP vaccines for influenza, which have shown both safety and efficacy in clinical trials. Importantly, the production costs for plant-based VLP vaccines are substantially lower than those for conventional vaccine manufacturing methods, potentially enabling more equitable global vaccine distribution [7,8,9,12,14,18]. Medicago’s vaccine was officially approved for human use in Canada by Canada Health in February 2022 and is marketed as COVIFENZ® [12,14].

These developments highlight the transformative potential of edible plant-based vaccines, which could revolutionize pandemic response through their cost-effectiveness, thermostability, and needle-free administration [7,8,12,14].

Future of edible vaccines and current research

Compared to traditional vaccines, oral vaccines have the potential to become a more effective method of disease prevention if they are properly designed and implemented [1,9]. The effectiveness of inducing an immune response via the oral route can be further increased by using appropriate adjuvants. However, more research in this area is needed to determine the most effective strategies for increasing immunogenicity [17]. They are characterized by low production costs due to the lack of complicated equipment, a good safety profile and high efficiency [1,2]. However, maintaining the quality and safety of genetically modified plants is a major challenge due to the risk of cross-contamination between non-genetically modified plants [1]. Unfortunately, there is a belief in the harmfulness of genetically modified plants in society. According to public opinion, crops are considered harmful to both the environment and the body. However, with the advancement of technology, genetically modified crops are becoming safer than ever before [1,2,9,17]. Despite the existing limitations, edible vaccines continue to attract considerable interest because they offer a promising alternative to conventional vaccines. Their longer shelf life compared to typical vaccines and the plant origin of the antigen envelope facilitate efficient transport of the antigen from the oral cavity to the intestines to induce an immune response. These are important arguments in favor of further development of edible forms of vaccination [4]. It is worth noting that vaccines are produced from plants that are subjected to clinical trials in accordance with the standards of the United States Investigational New Drug Research Application and in accordance with the principles of good agricultural practice [4]. Although there is currently no access to edible vaccines, the study by Garduño-González et al. (2022) indicates that in the future, the vaccine will be administered by eating a tomato [8,9]. According to the study by Sahoo et al. (2020), edible vaccines could also be produced from grass and plants such as coffee, which are often consumed by animals and humans. The study by Richter et al. (2000) predicts that proteins such as insulin, human growth hormone, and anti-hematopoietic proteins (e.g. factor VIII) will be used in the production of oral vaccines [7]. Edible vaccines may become important in the third world countries in the future, due to the low cost of transportation and storage and the possibility of administration without the use of a needle [3,4]. The time is coming when we will be able to obtain protection against pathogens by eating fruits and vegetables containing vaccines. They will become not only food, but also a preventive measure against infectious diseases (Tacket, 2007) [7]. In addition, these vaccines offer hope for combating future pandemics. Royal et al. conducted research on a SARS-CoV-2 vaccine candidate using plant-based production technology and tobacco mosaic virus nanoparticles. This discovery offers the possibility of creating a COVID-19 vaccine that is stable, easy to mass produce, and can be easily administered [14].

Conclusion

Edible vaccines are an innovative alternative to traditional vaccines, offering many potential benefits, especially in the context of global health challenges and limited access to healthcare in developing countries. Unlike injectable vaccines, edible vaccines are produced in plants or microorganisms and administered orally, eliminating the need for needles, medical personnel, and a cold chain. By inducing both mucosal and systemic immunity, they can effectively protect against infections as early as the pathogen enters the body.

The advantages of this technology include low production costs, ease of storage, safety of use, and high social acceptability, especially among children. An example of success in this area is the COVIFENZ® vaccine against COVID-19, approved in Canada, based on virus-like particles (VLPs) produced in the Nicotiana benthamiana plant.

However, the development of edible vaccines also faces significant challenges. These include difficulties in determining the appropriate dosage, the risk of immunological tolerance, degradation of antigens in the gastrointestinal tract, and social distrust of genetically modified organisms. Additionally, cooking some plant foods can destroy the active ingredients of the vaccine.

Despite these limitations, research on edible vaccines is progressing rapidly. It is expected that in the future they will be used not only in the prevention of infectious diseases, but also in the treatment of autoimmune diseases. Their potential as a cheap, easy-to-distribute, and safe means of health prevention means that they can play a key role in the global vaccination strategy, especially in the face of future pandemics.

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